L2 ANSWER 7 OF 13 MEDLINE
AN 95147974 MEDLINE
DN 95147974 PubMed ID: 7845465
TI **Alzheimer-type neuropathology** in transgenic mice overexpressing V717F beta-amyloid precursor protein.
CM Comment in: Nature. 1995 Feb 9;373(6514):476-7
Comment in: Nature. 1995 May 25;375(6529):285
AU Games D; Adams D; Alessandrini R; Barbour R; Berthelette P; Blackwell C; Carr T; Clemens J; Donaldson T; Gillespie F; +
CS Athena Neurosciences, Inc., South San Francisco, California 94080.
SO NATURE, (1995 Feb 9) 373 (6514) 523-7.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950316
Last Updated on STN: 19980206
Entered Medline: 19950303
AB Alzheimer's disease (AD) is the most common cause of progressive intellectual failure in aged humans. AD brains contain numerous amyloid plaques surrounded by dystrophic neurites, and show profound synaptic loss, neurofibrillary tangle formation and gliosis. The amyloid plaques are composed of amyloid beta-peptide (A beta), a 40-42-amino-acid fragment of the beta-amyloid precursor protein (APP). A primary pathogenic role for APP/A beta is suggested by missense mutations in APP that are tightly linked to autosomal dominant forms of AD. A major obstacle to elucidating and treating AD has been the lack of an animal model. Animals transgenic for APP have previously failed to show extensive AD-type neuropathology, but we now report the production of transgenic mice that express high levels of human mutant APP (with valine at residue 717 substituted by phenylalanine) and which progressively develop many of the pathological hallmarks of AD, including numerous extracellular thioflavin S-positive A beta deposits, neuritic plaques, synaptic loss, astrocytosis and microgliosis. These mice support a primary role for APP/A beta in the genesis of AD and could provide a preclinical model for testing therapeutic drugs.

L3 ANSWER 1 OF 1 MEDLINE
AN 96412254 MEDLINE
DN 96412254 PubMed ID: 8810256
TI **Correlative memory deficits**, Abeta elevation, and **amyloid plaques** in transgenic mice.
CM Comment in: Science. 1996 Oct 11;274(5285):177-8
Comment in: Science. 1997 Aug 8;277(5327):839-41
AU Hsiao K; Chapman P; Nilsen S; Eckman C; Harigaya Y; Younkin S; Yang F; Cole G
CS Department of Neurology, UMHC Box 295, 420 Delaware Street, University of Minnesota, Minneapolis, MN 55455, USA.
NC AG06656 (NIA)
AG9009 (NIA)
NS33249 (NINDS)
+
SO SCIENCE, (1996 Oct 4) 274 (5284) 99-102.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961106
Last Updated on STN: 19980206
Entered Medline: 19961024
AB Transgenic mice overexpressing the 695-amino acid isoform of human Alzheimer beta-amyloid (Abeta) precursor protein containing a Lys670 --> Asn, Met671 --> Leu mutation had normal learning and memory in spatial reference and alternation tasks at 3 months of age but showed impairment by 9 to 10 months of age. A fivefold increase in Abeta(1-40) and a 14-fold increase in Abeta(1-42/43) accompanied the appearance of these behavioral deficits. Numerous Abeta plaques that stained with Congo red dye were present in cortical and limbic structures of mice with elevated amounts of Abeta. The correlative appearance of behavioral, biochemical, and pathological abnormalities reminiscent of Alzheimer's disease in these transgenic mice suggests new opportunities for exploring the pathophysiology and neurobiology of this disease.

N 21341193 PubMed ID: 11447836
TI Modelling Alzheimer's disease in multiple **transgenic mice**.
AU Dewachter I; Moechars D; van Dorpe J; Tesseur I; Van den Haute C; Spittaels K; Van Leuven F
CS Experimental Genetics Group, Center for Human Genetics, Flemish Institute for Biotechnology (VIB), K.U. Leuven Campus, Gasthuisberg, B-3000 Leuven, Belgium.
SO BIOCHEMICAL SOCIETY SYMPOSIA, (2001) (67) 203-10.
Journal code: 7506896. ISSN: 0067-8694.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011214
AB We have reported **transgenic mice** with neuronal overexpression of the clinical mutant beta-amyloid precursor protein (APP) known as London, which develop an AD-related phenotype [Moechers, Dewachter, Lorent, Reverse, Baekelandt, Nadiu, Tesseur, Spittaels, Van den Haute, Checler, et al. (1999) J. Biol. Chem. 274, 6483-6492]. Characterized early symptoms (3-9 months) include disturbed behaviour, neophobia, aggression, hypersensitivity to kainic acid, hyposensitivity to N-methyl-D-aspartate, defective cognition and memory, and decreased long-term potentiation. Late in life, at 12-15 months, **amyloid plaques** develop in the brain and correlate with increased levels of beta-amyloid (A beta)40/42 (the 40- and 42-amino-acid forms of A beta). The formation of **amyloid plaques** is dissociated in time from and not involved in the early phenotype. Hyperphosphorylated protein tau is present but no tangle pathology is observed. In double-**transgenic mice**, i.e. APP/London x Presenilin 1, the increased production of A beta 42 results in **amyloid plaques** developing by the age of 6 months. **Transgenic mice** with overexpression of either human apolipoprotein E4 (ApoE4) or human protein tau in central neurons develop severe axonopathy in the brain and spinal cord. Progressive degeneration of nerves and muscles is demonstrated by motor problems, wasting and premature death. Tau is hyperphosphorylated but there is no formation of filaments or **neurofibrillary tangles**. The tangle aspect of AD pathology is still missing from all current transgenic amyloid models. Its implementation will require insight into the cellular signalling pathways which regulate the microtubule-stabilizing function by phosphorylation of neuronal tau.

L4 ANSWER 10 OF 14 MEDLINE
AN 1999131210 MEDLINE
DN 99131210 PubMed ID: 9932418
TI Neurodegenerative Alzheimer-like pathology in PDAPP 717V-->F **transgenic mice**.
AU Chen K S; Masliah E; Grajeda H; Guido T; Huang J; Khan K; Motter R; Soriano F; Games D
CS Athena Neurosciences, South San Francisco, California 94080, USA.. amyloid!kchen@uunet.uu.net
SO PROGRESS IN BRAIN RESEARCH, (1998) 117 327-34. Ref: 37
Journal code: 0376441. ISSN: 0079-6123.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990311
AB In summary, PDAPP mice overexpressing a mutation associated with some cases of familial early-onset AD express several of the major pathological hallmarks associated with AD. **Amyloid plaques** in PDAPP mice appear quite similar to A beta deposits in AD as shown by a variety of different antibodies and stains, and are of both the diffuse and compacted varieties. Additionally, a subset of these **amyloid plaques** appear to be neuritic plaques. Neurodegenerative changes, including the loss of synaptic and dendritic proteins, abnormal phosphorylation of cytoskeletal elements, subcellular degenerative changes, and the deposition of lysosomal and acute phase proteins has also been seen in PDAPP mouse brains. Reactive astrocytosis and microgliosis have also been observed in association with the **amyloid plaques** in the PDAPP mice. No **neurofibrillary tangles** or paired helical filaments have been found in the mice to date. It remains unknown whether mice are capable of generating these in a manner comparable to AD in less than two years. Extensive behavioral analyses are currently being performed in these mice, and preliminary results indicate that the PDAPP mice are significantly impaired on a variety of different learning and memory tests. In conclusion, the PDAPP mouse model doesn't display all the pathological hallmarks of AD, but it does display most of them in a robust manner that increases with age and gene dosage. Therefore, this transgenic model provides evidence that alterations in APP processing and A beta production can result in AD-like neuropathology, can contribute to a mechanistic understanding of AD (since examination of AD brains yields a static view, and we are unable to view the development of various pathological changes), as well as providing an useful animal model for the testing of various therapeutic interventions directed towards specific aspects of the neurodegenerative process.

L4 ANSWER 9 OF 14 MEDLINE
AN 2000005421 MEDLINE
DN 20005421 PubMed ID: 10537029
TI Progress toward valid transgenic mouse models for Alzheimer's disease.
AU Guenette S Y; Tanzi R E
CS Department of Neurology, Massachusetts General Hospital, Charlestown 02129, USA.. guenette@helix.mgh.harvard.edu
SO NEUROBIOLOGY OF AGING, (1999 Mar-Apr) 20 (2) 201-11. Ref: 106
Journal code: 8100437. ISSN: 0197-4580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991229
AB A transgenic mouse model for Alzheimer's disease (AD) should mimic the age-dependent accumulation of beta-**amyloid plaques**, **neurofibrillary tangles**, neuronal cell death as well as display memory loss and behavioral deficits. Age-dependent accumulation of A beta deposits in mouse brain has been achieved in mice overexpressing mutant alleles of the amyloid precursor protein (APP). In contrast, mice bearing mutant alleles of the presenilin genes show increased production of the A beta42 peptide, but do not form amyloid deposits unless mutant alleles of APP are also overproduced. Furthermore, the onset of A beta deposition is greatly accelerated, paralleling the involvement of presenilins in early onset AD. Studies of APP and presenilin **transgenic mice** have shown 1) the absence of a requirement for a maturation step in dense core plaque formation, 2) evidence that beta-amyloid deposition is directed by regional factors, and 3) behavioral deficits are observed before A beta deposition. Crosses of APP **transgenic mice** with mice modified for known AD risk factors and "humanizing" the mouse may be necessary for complete replication of AD.

L4 ANSWER 12 OF 14 MEDLINE
AN 95053861 MEDLINE
DN 95053861 PubMed ID: 7964589
TI Modeling Alzheimer's disease in **transgenic mice**.
AU Duff K
CS Department of Psychiatry, University of South Florida College of Medicine.
SO JOURNAL OF THE FLORIDA MEDICAL ASSOCIATION, (1994 Sep) 81 (9) 625-8. Ref: 30
Journal code: 7505604. ISSN: 0015-4148.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199412
ED Entered STN: 19950110
Last Updated on STN: 19980206
Entered Medline: 19941229
AB Alzheimer's disease is a common neurodegenerative disorder of unknown etiology characterized by the accumulation of beta **amyloid plaques** and **neurofibrillary tangles** in the brain. Attempts have been made to engineer an animal model of the disease using a variety of transgenic approaches. So far the models have only been partially successful. The methods used and the models generated are discussed.

L4 ANSWER 14 OF 14 MEDLINE
AN 92086045 MEDLINE
DN 92086045 PubMed ID: 1793460
TI **Amyloid plaques, neurofibrillary tangles** and neuronal loss in brains of **transgenic mice** overexpressing a C-terminal fragment of human amyloid precursor protein.
CM Comment in: Nature. 1991 Dec 12;354(6353):432-3
Retraction in: Kawabata S, Higgins GA, Gordon JW. Nature 1992 Mar 5;356(6364):23 and Nature 1992 Mar 19;356(6366):265
AU Kawabata S; Higgins G A; Gordon J W
CS Department of Geriatrics and Adult Development, Mt Sinai Medical Center, New York, New York 10029.
SO NATURE, (1991 Dec 12) 354 (6353) 476-8.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(RETRACTED PUBLICATION)
LA English
FS Priority Journals
EM 199201
ED Entered STN: 19920209
Last Updated on STN: 19980206
Entered Medline: 19920121
AB Alzheimer's disease (AD) affects more than 30% of people over 80 years of age. The aetiology and pathogenesis of this progressive dementia is poorly understood, but symptomatic disease is associated histopathologically with **amyloid plaques, neurofibrillary tangles** and neuronal loss primarily in the temporal lobe and neocortex of the brain. The core of the extracellular plaque is a derivative of the amyloid precursor protein (APP), referred to as beta/A4, and contains the amino-acid residues 29-42 that are normally embedded in the membrane-spanning region of the precursor. The cellular source of APP and the relationship of its deposition to the neuropathology of AD is unknown. To investigate the relationship between APP overexpression and amyloidogenesis, we have developed a vector to drive expression specifically in neurons of a C-terminal fragment of APP that contains the beta/A4 region, and have used a transgenic mouse system to insert and express this construct. We report here that overexpression of this APP transgene in neurons is sufficient to produce extracellular dense-core **amyloid plaques, neurofibrillary tangles** and neuronal degeneration similar to that in the AD brain.

L4 ANSWER 12 OF 14 MEDLINE
AN 95053861 MEDLINE
DN 95053861 PubMed ID: 7964589
TI Modeling Alzheimer's disease in **transgenic mice**.
AU Duff K
CS Department of Psychiatry, University of South Florida College of Medicine.
SO JOURNAL OF THE FLORIDA MEDICAL ASSOCIATION, (1994 Sep) 81 (9) 625-8. Ref: 30
Journal code: 7505604. ISSN: 0015-4148.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199412
ED Entered STN: 19950110
Last Updated on STN: 19980206
Entered Medline: 19941229
AB Alzheimer's disease is a common neurodegenerative disorder of unknown etiology characterized by the accumulation of beta **amyloid plaques** and **neurofibrillary tangles** in the brain. Attempts have been made to engineer an animal model of the disease using a variety of transgenic approaches. So far the models have only been partially successful. The methods used and the models generated are discussed.

L4 ANSWER 13 OF 14 MEDLINE
AN 92204240 MEDLINE
DN 92204240 PubMed ID: 1552948
TI **Amyloid plaques, neurofibrillary tangles** and neuronal loss in brains of **transgenic mice** overexpressing a C-terminal fragment of human amyloid precursor protein.
CM Retraction of: Kawabata S, Higgins GA, Gordon JW. Nature 1991 Dec 12;354(6353):476-8
AU Kawabata S; Higgins G A; Gordon J W
SO NATURE, (1992 Mar 19) 356 (6366) 265.
Journal code: 0410462. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT (RETRACTION OF PUBLICATION)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920427

L7 ANSWER 1 OF 7 MEDLINE
AN 2002366817 IN-PROCESS
DN 22106566 PubMed ID: 12111445
TI Potential neurotoxic inflammatory responses to Abeta vaccination in humans.
AU Munch G; Robinson S R
CS Neuroimmunological Cell Biology Unit, Interdisciplinary Centre for Clinical Research (IZKF), University of Leipzig, Federal Republic of Germany.
SO JOURNAL OF NEURAL TRANSMISSION, (2002 Jul) 109 (7-8) 1081-7.
Journal code: 9702341. ISSN: 0300-9564.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020712
Last Updated on STN: 20020712
AB SUMMARY: Studies in transgenic mouse models of Alzheimer's disease suggested the development of a vaccine that would induce the production of **antibodies** against **amyloid-beta** (Abeta) peptide, which in turn would stimulate microglia to phagocytose and remove senile plaques. However, some patients in the human **clinical trials** developed symptoms of brain inflammation, demonstrated by lymphocyte infiltration and elevated protein levels. These parameters are indicative of a breakdown of the blood-brain-barrier and entry of T-cells into the brain. Abeta-specific activated T-helper cells have the potential to amplify the existing pro-inflammatory conditions that are present in the brains of Alzheimer's disease patients. Cytotoxic T-cells might even attack the **amyloid** precursor protein which is present on the surface of many cells, including neurons. Before undertaking further vaccination trials there is a need to re-assess the risks associated with Abeta vaccination and with the therapeutic containment of a neuroinflammatory response. These risks may not be justified in the light of recent studies which have shown the efficacy of conventional, low-risk treatments in slowing the progress of AD.

See also Bloss Immunotreat Ady
NEJM 341(22):1694 J'1999